Small Bowel Adenocarcinoma

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Abstract

Small bowel adenocarcinoma is a clinically and anatomically distinct gastrointestinal cancer that lacks prospective data to support its optimal management. Patients with inflammatory bowel disease and inherited conditions that cause gastrointestinal polyps are at especially high risk. Due to a lack of effective surveillance programs resulting in missed or delayed diagnoses only when symptoms develop, this disease is generally discovered at an advanced stage. Surgical resection is the only treatment modality with a chance of cure. Currently accepted treatment considerations are often generalized from large bowel and pancreatic–biliary cancers, due to some anatomic and clinical parallels. Additional research, however, is desperately needed to characterize the unique molecular differences of this disease to better prognosticate patients and establish rational clinical trials that would improve their outcomes.

Keywords

- small bowel adenocarcinoma
- small intestinal adenocarcinoma
- small intestinal cancer
- small bowel malignancies
- small bowel cancer

Epidemiology

Cancer of the small intestine is uncommon. It represents only 0.6% of all new cancer cases in the United States each year.[1] There will be an estimated 10,090 cases diagnosed in the United States in 2016, and 1,330 Americans are estimated to die of this disease on an annual basis.[1] It is less common than melanoma, thyroid cancer, or kidney cancer, but the incidence is rising steadily. While the incidence of colorectal cancer is declining, it is still 10 times more common than small intestinal cancers. Despite being the longest segment of mucosa in the gastrointestinal tract, often longer than 10 feet, carcinoma of the small intestine is less prevalent than either esophageal or gastric cancers. Considering all small bowel malignancies, neuroendocrine tumors are the most common (37.4%), but adenocarcinomas closely follow at 36.9%.[2] Sarcomas and lymphomas involving the small intestine are less common but well recognized. The most common location of small bowel adenocarcinoma (SBA) is in the duodenum (49–58%), followed by jejunum (19–29%), and ileum (10–15%);[3–6] this is unlike neuroendocrine tumors, which are more commonly found in the ileum.

Demographics seen in SBA include a median age of ~62 years at presentation, or often sixth decade of life, and 53 to 62% male sex,[3,7,8] which also reflects Surveillance, Epidemiology, and End Results statistics for all small bowel cancers. It is seen in all races, with those of black race being more affected and Asian race, less affected. Age is the only demographic that has a direct association with the incidence of SBA.[9] There may also be a trend toward older patients older than the age of 60 years for duodenal adenocarcinomas,[3] but there is generally no statistically significant association between tumor location and demographic factors, such as age, sex, or race.[7]

While SBA can arise sporadically, it is frequently found in patients with specific genetic syndromes, or those with preexisting gastrointestinal diseases. ►**Table 1** lists these associated medical conditions, their risk of SBA, and general guidelines for surveillance. All four genetic syndromes involved are autosomal dominant disorders. In familial adenomatous polyposis (FAP), patients can develop precancerous polyps in the gastrointestinal tract more often in the colon, but also the duodenum, which can give rise to duodenal adenocarcinomas. The prevalence of duodenal polyps in this population can be as high as 90%, with a relative risk of 330, or up to 5% lifetime risk of duodenal adenocarcinoma.[10] Screening with double balloon enteroscopy in addition to routine upper endoscopy has been advocated to reduce this

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Table 1 Gastrointestinal conditions and their risk of SBA[10–12,14,39,68–70]

Disease condition	Gene defects or association	Incidence of medical condition	Relative risk of SBA (95% CI)	Lifetime risk of SBA	Average age of SBA at diagnosis	Surveillance recommendations for SBA	Guideline sources
Familial adenomatous polyposis	*APC*	2.3–3.2 cases per 100,000	330 (132–681)	3–5%	44	Colonoscopy every 1–2 y at puberty, upper endoscopy every 1–5 y at the age of 25–30 y, and additional small bowel imaging, if duodenal adenomas are detected	ACG
Lynch's syndrome, or hereditary nonpolyposis colorectal cancer	*MSH2*, *MSH6*, *MLH1*, and *PMS2*	1 in 370	291 (71–681)	1–4%	46–51	Colonoscopy every 1–2 y at the age of 20–25 y, and upper endoscopy every 3–5 y at the age of 30–35 y	ACG
Peutz–Jeghers' syndrome	*STK11*	0.5–4 cases per 100,000	500 (220–1,306)	1.7–13%	37–42	Colonoscopy, video capsule endoscopy, and upper endoscopy every 3 y at the age of 18 y and possibly one time at the age of 8 y	ACG
Juvenile polyposis syndrome	*BMPR1A* and *SMAD4*	<1 case per 100,000	Undefined	Undefined	54	Undefined	None
Crohn's disease	Many loci	201 cases per 100,000	30–60 (15–609)	0.2–2.2%	30–40	Colonoscopy 8–10 y after disease diagnosis but no guidelines for small bowel cancer	ACG
Celiac disease	HLA-DQ2, HLA-DQ8	1 in 100	60–80 (7–240)	<1%	Undefined	Undefined	None

Abbreviations: ACG, American College of Gastroenterology; APC, adenomatous polyposis coli; CI, confidence interval; HLA, human leukocyte antigen; SBA, small bowel adenocarcinoma.

risk. Varied penetrance due to different mutations in the same gene may result in atypical polyp morphology and a varied distribution of polyps.

Similarly, patients with Lynch's syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) are vulnerable to the development of various cancers, including relative risk and lifetime risk of SBA that can range from 25 to 297 and 1 to 4%, respectively, depending on the specific mismatch repair mutation.[11] Upper endoscopy for asymptomatic patients is not well supported in this population, but the American College of Gastroenterology (ACG) does recommend offering upper endoscopy every 3 to 5 years to those older than the age of 30 to 35 years.[12] Surveillance using video capsule endoscopy has detected duodenal adenocarcinoma and adenomatous polyps in asymptomatic patients, which could be managed with solely upper endoscopy techniques.[13]

Peutz–Jeghers' syndrome (PJS) also has elevated risk of gastrointestinal cancers that arise from adenomas and hamartomas, with relative risk as high as 520, and lifetime risk of 13%.[14] Even so, most hamartomas are generally benign. This genetic syndrome is also associated with hyperpigmentation in the mouth, lips, hands, and feet. Surveillance for stomach, small bowel, and colorectal cancers is recommended before the age of 18 years, but there is no clear consensus on the optimal age and interval. Finally, in juvenile polyposis syndrome (JPS), patients can have a range of benign polyps in the gastrointestinal tract, with occasional progression to malignancies that are more commonly found in the colon and stomach. While it is thought to be associated with SBA, the relative risk is not known, due to a limited number of cases.

There is also a recognized association of SBA with both Crohn's disease and celiac disease,[3,15,16] possibly due to chronic inflammation or immune system dysregulation. In one study, up to 8.4% of patients with SBA had coexistent Crohn's disease.[17] The risk seems to increase with disease chronicity and activity in the small intestines, and patients may develop cancer at a young age if they have had inflammatory bowel disease since childhood. The most commonly affected location is in the ileum, which is commonly involved in Crohn's disease. In celiac disease, SBA is not as well recognized as lymphoma, but when it occurs, it is found often in the jejunum. Diet modifications often can reverse the disease process; thus, SBA is infrequently observed in this disease, as compared with Crohn's disease. Invasive diagnostic procedures used in both diseases may incidentally discover precancerous lesions and early-stage cancers, which are more likely to be curable. For this reason, ileal intubation during colonoscopy is especially important for patients with Crohn's disease, as it accomplishes both disease monitoring and cancer surveillance. Nevertheless, there are no specific surveillance guidelines for SBA in either disease.

Modifiable social risk factors have been reported as well, and there are several distinctions from colorectal cancer. Cigarette smoking, interestingly, has not been found to be associated with small intestinal cancers.[18,19] There seems, however, to be an association with high alcohol intake, particularly from beer and spirits, but not wine, though

the effect is likely small.[19] Dietary factors are generally weakly or not at all associated with SBA. High saturated fat diets, for example, are associated with small intestinal cancer, but diets high in red and processed meats have not been convincingly shown to be associated with small bowel carcinogenesis, as in colorectal cancer.[20] Whole grains and grain fiber are associated with a protective effect against SBA.[21] The low number of cases reported for this disease, however, limits the ability to study heterogeneous variables, such as specific diets and food items. Finally, elevated body mass index has a weak association with small intestinal cancer.[5,18] An alternate study proposed that abdominal obesity, rather than other types of obesity might be associated with SBA.[22] Overall, there is no strong evidence to support specific diet or lifestyle recommendations to prevent the development of SBA.

At the time of diagnosis of SBA, ~65 to 73% of patients will have operable disease, which can be divided further to 4 to 6% at stage I, 20 to 27% at stage II, and 24 to 39% at stage III, according to the American Joint Committee on Cancer (AJCC) staging guidelines.[4,23] The majority, however, will have at least stages III and IV disease. Unresectable disease, due to advanced cancer stage or medical comorbidities, is considered incurable. SBA, especially in the duodenum, has a poorer prognosis compared with colorectal cancer, with overall 5-year survival as low as 26 to 41%, and median overall survival (OS) of 20 to 38 months.[2,23,24] ►**Table 2** shows both cancer-specific survival and OS by AJCC staging. The extent of resection and lymph node retrieval, resection at experienced centers, and lower stage are all associated with improved survival.[4,11,24,25] Patients with specific genetic syndromes are generally diagnosed at a younger age and are, therefore, unlikely to have comorbidities that would interfere with aggressive treatment options. There is no data to suggest they would have worse prognosis, but they can certainly harbor second or even third malignancies. Patients who have Crohn's disease have a similar prognosis to those who do not, but may be diagnosed at an earlier stage as well.[17] Patients with metastatic SBA have an overall 5-year survival of 11 to 19%,[23,24] which is similar to metastatic colorectal cancer. Patients with colorectal cancer, however, overall have 5-year survival that improved from 50% in 1977 to 66% in 2011.[1] Thus, better diagnostic modalities and therapies are urgently needed to improve outcomes in small SBA.

Table 2 Overall survival of small bowel adenocarcinoma by stage[4,23,24]

AJCC staging	Cancer-specific survival	Overall survival
I	85–87%	57–66%
II	61–75%	43–50%
III	40–67%	31–42%
IV	17–46%	5–19%

Abbreviation: AJCC, American Joint Committee on Cancer.

Genetics and Molecular Biology

The pathogenesis of SBA is not well understood, due to the rarity of this type of cancer. Much of what is known is extrapolated from either colorectal cancer or pancreatic–biliary cancers. By comparing markers of proliferation among normal mucosa, adenomatous polyps, and invasive adenocarcinoma, many have postulated that the adenoma-to-carcinoma sequence applies to SBA.[26,27] Research studies that examine molecular pathways in SBA do not necessarily separate tumor samples from patients with sporadic mutations from those with germ-line mutations because it is believed that patients with genetic syndromes are simply one step further along the adenoma-to-carcinoma sequence. In fact, much of what we know stems from molecular and clinical analysis of samples from patients with germ-line mutations, such as FAP and Lynch's syndrome. There is, however, also speculation that the pathogenesis of duodenal adenocarcinoma may be different from the rest of the small intestine, as its histology can reflect that of gastric and biliary tract cancers; therefore, mutations common in those cancers have also been explored in SBA.

There are several important pathways that can lead to invasive SBA. First, as understood from FAP, the adenomatous polyposis coli (APC) mutation, whether hereditary or sporadic, leads to upregulation of the Wnt signaling pathway. APC deactivation is believed to be one of the first steps in the adenoma-to-carcinoma sequence. APC normally binds to B-catenin and enhances its degradation via phosphorylation, but when APC is dysfunctional, intact B-catenin enters the nucleus and activates transcription factors for genes that promote cell proliferation. While this is commonly observed in colorectal cancer, it is seen only in 13 to 19% of SBA.[28,29] The lower frequency in SBA suggests there may be other mechanisms needed to trigger the first steps of tumorigenesis; there could also occasionally be a gain of function in the *B-catenin* gene, leading to B-catenin accumulation in the cell nucleus.[11] Both APC dysfunction and B-catenin overactivation lead to increased nuclear expression of B-catenin, which can be measured by immunohistochemistry. This common outcome is observed in up to 40% of cases.[8] APC mutation is also associated with mutations in *ERBB2*/*HER2*, a receptor tyrosine kinase responsible for cell growth, and *FBXW7*, a protein involved in ubiquitin degradation of cyclin E in the cell cycle; it is unclear, however, how these mutations interact with APC in SBA.[29]

Similarly, as understood from Lynch's syndrome, mismatch repair protein dysregulation is also one of the first steps in the tumorigenesis of colorectal cancer. In fact, tumors with mismatch repair protein deficiency are unlikely to be associated with key cancer-predisposing conditions, such as with Crohn's disease, celiac disease, and FAP.[30] Mismatch repair protein deficiency can occur in 7 to 35% of SBA,[8] but abnormal *MSH2* and *MSH6* occur much more frequently, compared with colorectal cancer.[30] Even patients without a family history of Lynch's syndrome can have deficiencies in this pathway, with the exception of *MLH1*, which has not been observed to be sporadic.[30] Defects in *MSH1*, *MSH2*, *MSH6*, and *PMS2*, either as direct gene mutation or promoter methylation, are all

associated with microsatellite instability, which are specific DNA repeats that reflect the ability to accumulate multiple mutations, due to the lack of correcting mechanisms. The four mismatch repair proteins typically form a protein complex that recognizes mismatched bases that may occur during DNA replication or from DNA damage. Thus, missing even one of the four proteins can result in microsatellite instability, as well as mutations in proto-oncogenes and tumor suppressor genes in key carcinogenesis pathways, such as Wnt and *KRAS* pathways. Specifically, *KRAS* and *BRAF* mutations have been found to be more prevalent in tumors that have more chromosome instability.[31] *ERBB2*/*HER2* mutations are also found more frequently in tumors with mismatch protein deficiency.[29] Mismatch repair protein deficient tumors have been compared between small bowel and colorectal adenocarcinoma, and their clinical and pathological characteristics are similar.[30]

Other genes associated with known genetic syndromes, such as *STK11*, that codes a serine/threonine kinase in cell homeostasis pathway in PJS[14] and *SMAD4* and *BMPR1A* that code membrane receptors in transforming growth factor beta (TGF-B) pathway in JPS, may also have a role in the polyp formation that could lead to invasive cancer. Sporadic mutations in those without the genetic syndrome, however, are not well understood. Even so, sporadic deletions in chromosome 18q21 have been associated with *SMAD4* abnormalities in small intestinal adenocarcinomas.[32] TGF-B signaling pathway may also be an important latter step of adenoma to carcinoma sequence. ►**Table 3** summarizes the frequency of key mutations in small bowel carcinogenesis and their respective citations.

Gene sequencing has confirmed mutations in other well-known proto-oncogenes and tumor suppressor genes not specific to gastrointestinal cancers. For instance, abnormal *p53* is frequently observed (41–42%) and is associated with poor prognosis.[29,33–35] Alteration of *p53* is considered a late step in the adenoma-to-carcinoma sequence, as no additional mutations are likely needed to complete carcinogenesis, given its profound tumor suppressor activity. Another tumor suppressor, *p16*, or *CDKN2A*, which inhibits the cell cycle, is also increased in SBA.[34] Furthermore, *KRAS*, a proto-oncogene, is frequently mutated in SBA, with rates as high as 43%, but *BRAF* mutations are not often seen.[29,35] Constitutively active *KRAS* is thought to be in the intermediate step of adenoma-to-carcinoma sequence. Resistance to anti-*EGFR*-based therapy, such as cetuximab and panitumumab in SBA is not known. *EGFR* mutations are also observed in 4 to 8% of SBA, but it is unclear if targeted agents could be effective for those who have the *exon 19* deletion or *exon 21 L858R* mutation.[36] The low frequency of *BRAF* mutations in SBA also precludes use of *BRAF* and *MEK* inhibitors. *ERBB2*/*HER2* gene, in contrast, has been proposed as a potential target, as up to 12% of SBA have this target.[29] Interestingly, *ERBB2*/*HER2* and *p53* may be mutually exclusive, as they are not observed to coexist in the same tumor.[29] Additional mutations, such as *IDH1*, *CDH1*, *KIT*, *FGFR2*, *FLT3*, *NPM1*, *PTEN*, *MET*, *AKT1*, *RET*, and *NOTCH1*, have also been reported, but further characterization in SBA is needed.[33] Many of these mutations are related to known genetic syndromes, but those syndromes are not known to be specifically associated SBAs.

Immunology and Pathogenesis

Chronic inflammation may also be important in the carcinogenesis of SBA. This hypothesis may explain how certain gastrointestinal diseases and social risk factors are associated with malignancy. In inflammatory bowel disease, particularly Crohn's disease, there is an abnormal response to intestinal organisms and perhaps environmental exposures, which leads to inflammation in parts of the gastrointestinal tract. For this reason, SBA associated with Crohn's disease often occurs in the ileum, rather than in other locations.[17] Inflammation may trigger cytokines that promote cell growth, but also damage the epithelial surface, which can directly cause dysplasia, and may also allow carcinogens to pass through intercellular junctions to the cell microenvironment. Dysplastic cells are then thought to accumulate mutations in *KRAS*, *p53*, and mismatch repair proteins, which are all known drivers in the adenoma-to-carcinoma sequence.[37,38] The molecular biology is indeed similar between sporadic and Crohn's-associated adenocarcinoma of the small intestines, but the tumor location, clinical characteristics, and pathology are quite different.[37] While there are many loci that have been implicated in Crohn's disease, their direct contribution to disease activity and cancer risk is not entirely clear. Specific therapy for inflammatory bowel disease, such as anti-TNF-based therapy, is unlikely to have cancer-specific activity, but limiting inflammation may reverse dysplasia and decrease the risk of carcinogenesis.

In celiac disease, there is a similar inflammatory process, whereby dysplasia develops from the flattened mucosa as a

Table 3 Molecular abnormalities and their frequency in small bowel adenocarcinoma

References	*N*	*p53*	*KRAS*	*dMMR*	*APC*	*B-catenin*	*ERBB2*/*HER2*	*BRAF*
Xia et al (2017)[30]	71	–	31%	8.5%	–	–	–	0%
Alvi et al (2015)[33]	28	54%	42%	21%	7.1%	–	10%	3.5%
Laforest et al (2014)[29]	83	41%	43%	21%	13.2%	–	8.4%	6.0%
Aparicio et al (2013)[35]	63	42%	43%	23%	–	20%	3.2%	2.5%
Overman et al (2010)[43]	54	–	–	35%	–	–	1.7%	–
Zhang et al (2006)[28]	26	54%	–	8%	31%	19%	–	–

Abbreviation: APC, adenomatous polyposis coli.

result of repetitive exposure to gluten.[39] An immune evasion aspect, due to the lymphocyte dysfunction that causes celiac disease activity, however, likely exists as well. For this reason, patients with celiac disease have higher odds of extraintestinal lymphoma, pancreatic–biliary cancers, and esophageal adenocarcinoma.[39] While celiac disease is associated with human leukocyte antigen DQ2 and DQ8, these have not been directly correlated with SBA. Immune regulation within SBA is poorly understood, and there is no current knowledge of the role of checkpoint mechanisms, such as *PD-1* with *PD-L1* and *CTLA4* with *B7*, in SBA.

There are several theories regarding the reason why SBA is much less common than colorectal cancer, despite the longer length and larger surface area of the small intestine. For one, lymphoid tissue and immunoglobulin A are much more abundant in the small intestines, and may contribute to better immune recognition of abnormal and dysplastic cells. The enzymes produced in the small intestines may also provide protective effect against food carcinogens. There is also rapid turnover of epithelial cells, which may overcome damage from carcinogens. Furthermore, the contents in the small bowel are generally more alkaline and dilute and have lower concentration of bacteria and carcinogens, due to rapid transit.[40] In addition, the microbiome in both locations within the bowel also differ, and may have varying protective effects depending on their luminal environment.

Clinical Presentation and Diagnosis

Most patients have an insidious presentation until the tumor is large enough to cause alarming symptoms, and, as a result, the diagnosis is often delayed. Specific symptoms can include abdominal pain, dyspepsia, change in bowel habits, diarrhea, nausea, vomiting, bloating, fatigue, generalized weakness, weight loss, and gastrointestinal bleeding, but abdominal pain is the most common.[3,4,41] Iron deficiency anemia from occult gastrointestinal loss may result in fatigue, generalized weakness, pallor, and shortness of breath on exertion. Specific complications can also occur, depending on the location of the tumor. Duodenal adenocarcinoma can lead to biliary obstruction, which can cause right upper quadrant pain, jaundice, and even cholangitis. Tumors in other parts of the small bowel can lead to gastric outlet and small bowel obstruction, which can lead to refractory nausea/vomiting, abdominal pain, inability to pass gas, perforation, and even peritonitis. Other more common disease processes, such as abdominal adhesions, cholelithiasis, pancreatitis, peptic ulcer disease, inflammatory bowel disease, diverticular diseases, and appendicitis, can explain many of these symptoms, thus further delaying the diagnosis of SBA.

Some patients may have early detection of invasive adenocarcinoma as part of a screening program, due to their genetic condition or inflammatory bowel disease. They are often diagnosed from esophagogastroduodenal endoscopy, video capsule endoscopy, or colonoscopy. Pediatric scopes or thinner fiber-optic scopes provide a better examination of the duodenum and proximal jejunum. In addition, single balloon enteroscopy or push enteroscopy can also visualize down to the jejunum. Newer techniques, using double balloon enteroscopy, may be able to examine further down the small intestines. Similarly, colonoscopy can often include examination of the ileum, and with push enteroscopy techniques, one can examine a longer segment of the ileum. This is especially useful in patients with inflammatory bowel disease who are already getting routine colonoscopy to evaluate for both ileal and colonic diseases and cancer surveillance. Combining ultrasound with endoscopy allows visualization of localized lymph nodes, although high-quality computed tomography (CT) scans are more helpful in determining resectability. Furthermore, it is not uncommon that symptomatic SBAs are unexpectedly diagnosed from a CT scan while looking for other more common disease processes. Magnetic resonance imaging (MRI) of the abdomen may better visualize the small bowel, and has been used in inflammatory bowel disease to evaluate for inflammation, fluid collections, stenosis, and fistulas. Cross-sectional imaging, whether CT or MRI, can also detect distant metastases, with the liver being the most common site.[4,6] In general, CT chest, abdomen, and pelvis with contrast are standard imaging modalities to complete staging, while positron emission tomography scan has not been validated in SBA and is likely unnecessary. Brain imaging is also likely unnecessary in asymptomatic patients.

The differential diagnosis of small bowel tumors may include benign and malignant lesions. Benign lesions may include adenomas, hamartomas, leiomyomas, and fibromas. Malignant lesions can also include lymphomas, leiomyosarcomas, carcinoid, gastrointestinal stromal tumors, and metastases, such as from melanoma, ovarian, lung, or other gastrointestinal cancers. Consultations with surgery and gastroenterologists are crucial in obtaining optimal tissue for diagnosis and addressing impending complications from symptomatic small bowel tumors. In fact, laparotomy, rather than endoscopy, has been observed to make histological diagnosis in up to 56% of cases.[3] This observation may reflect the difficulty in reaching primary tumor site with endoscopy and the often advanced presentation that requires surgical intervention. CEA and CA19-9 are serum tumor markers that can be elevated, but are not specific in SBAs, and are thus only helpful in following disease progression, rather than in making the diagnosis.

SBA can vary in histological presentation, depending on the location of the tumor. An intermediate grade of differentiation is the most common, reaching ~47 to 70%.[3,23,42–44] Mucinous features can occur in 28 to 42% of tumors,[30,43] and signet cell features can be found in 23 to 37% of tumors.[4,30] With respect to immunophenotype, lower gastrointestinal adenocarcinoma typically stains positive for *villin*, *CK20*, and *CDX2*, but negative for *CK7*. Duodenal tumors, however, can sometimes have gastric and pancreatic–biliary phenotypes in both morphology and immunohistochemistry. For this reason, *CK7* can be positive in 31% of tumors, and *CK20* can be negative in 43% of tumors.[43] Pancreatic–biliary tract cancers tend to be *CK7* and *CDX2* positive and sometimes *CK20* negative. Gastric phenotypes in SBA can stain positive for *MUC5AC*, but negative for *MUC1*, which is a marker for

intestinal phenotype.[8,45] Occasionally, poorly differentiated tumors can have very uncharacteristic markers, even negative for *CDX2*. As SBAs are usually diagnosed from pathology of the primary tumor, rather than from the metastatic site, an accurate diagnosis can be made with histology and cross-sectional imaging in the right clinical setting, even if the immunophenotype is atypical.

SBA follows tumor node metastasis staging as established by AJCC, most recently the seventh edition published in 2010. Stage I includes T1 and T2 lesions, which invade no further than muscularis propria. Stage II includes both T3 and T4 lesions, which invade into the subserosa and nearby organ and structures, but still have negative regional lymph nodes. Stage III includes any T stage and at least one positive regional lymph node. Stage IIIB includes tumors with four or more regional lymph nodes. Distant metastases define stage IV disease. Details of the staging scheme can be found on the AJCC Web site, www.cancerstaging.org.

Surgical Therapy

Surgical resection of early-stage SBA is the only treatment modality that has definite survival benefit.[23] The location of the tumor, however, may present special surgical challenges. For duodenal tumors, most patients will need a pancreaticoduodenectomy, or a Whipple's procedure, especially if the tumor is in the second portion of the duodenum. More recent studies, however, have demonstrated that a more conservative procedure with segmental resection does not impact survival, compared with traditional Whipple's resection, which is potentially more risky and morbid.[24,46] This observation suggests that duodenal adenocarcinomas are biologically distinct from pancreatic and ampullary adenocarcinomas, despite the anatomic proximity. Patients with duodenal adenocarcinoma undergoing segmental resection have shorter length of stay and lower postoperative mortality, compared with those undergoing a Whipple's procedure.[24] Thus, patients with adenocarcinoma in the first, third, and fourth segments of the duodenum may be considered for segmental resection if negative surgical margins can be achieved. Distal duodenal tumors may also be resected with pylorus-conserving procedures. Jejunal and ileal tumors can generally be treated with segmental resection, but wide excision is occasionally limited by proximity to mesenteric vasculature. Distal ileal disease may also require right hemicolectomy to achieve adequate resection. The surgical plan must be carefully considered regarding the tumor location, potentially involved organs, and the patient's comorbidities and fitness for surgery. All in all, data show that up to 80.1% of patients with nonmetastatic disease undergo resection.[2]

With respect to resection of the primary tumor, the surgeon must ensure all potential disease is resected. Several studies have shown the importance of achieving negative surgical margins[44,47] and adequate lymphadenectomy.[48,49] Frozen sections done intraoperatively can ensure margins are negative before closing the patient. Even so, microscopic disease could be left behind, particularly in the retroperitoneum or surrounding major vasculature. With regard to lymphadenectomy, negative lymph node status is correlated with better prognosis, and positive lymph node status can help the medical oncologist counsel patients regarding adjuvant chemotherapy.[50] Despite no national guidelines regarding the minimum number of lymph nodes in lymphadenectomy, most experts recommend 12 lymph nodes, as extrapolated from colorectal cancer. Some experts, however, also hypothesize 15 lymph nodes or more may be appropriate for duodenal tumors, using data from gastric cancer. Nevertheless, 18 to 44% of patients have only six or fewer lymph nodes examined.[24,49,50] Of note, T3 and T4 lesions are more highly associated with regional lymph node metastases.[50]

Metastasectomy may be considered for single liver metastasis, but the benefit of resection in limited metastatic disease is largely derived from colorectal cancer literature. The small intestinal lymphatic system generally drains into the portal venous system, and one would expect the first site of metastasis to be the liver. Metastasectomy in other organs, such as the lung or distant lymph nodes is not recommended as initial management because of high risk of microscopic metastases in other locations not yet visualized by cross-sectional imaging. Palliative chemotherapy would be the treatment of choice in these cases. The first recurrence after surgical resection often occurs in residual regional lymph nodes or distant organs, rather than at the anastomotic site, except in cases with positive margins,[25,44,51] highlighting the need for adequate resection margins and lymphadenectomy and close surveillance for locally advanced tumors.

Furthermore, peritoneal spread is not uncommon, particularly in locally advanced and perforated tumors. Although controversial there may be a role for cytoreductive surgery and intraperitoneal chemotherapy, especially for those without other distant metastases.[52,53] Cytologic evaluation of ascites is typically performed preoperatively or perioperatively to confirm peritoneal spread. The surgeon will then examine and identify all visible tumor and perform a cytoreductive surgery with the goal of R0 resection, followed by hyperthermic intraperitoneal chemotherapy (HIPEC) (see the article on HIPEC for additional details).

Overall, definitive surgical management for the primary tumor is generally not recommended in stage IV disease, due to the overall poor prognosis in metastatic SBA, even with palliative chemotherapy. Palliative surgeries, however, can potentially be offered to patients. For duodenal tumors, gastrojejunostomy or duodenal jejunostomy, either via Roux-en-Y or loop fashion could alleviate gastric outlet obstruction. Alternatively, palliative duodenal or jejunal stents could be considered by advanced gastrointestinal endoscopists. Bypass feeding tubes are unlikely to improve quality of life and survival. Furthermore, choledochojejunostomy could relieve biliary obstruction, and double bypass procedures are sometimes done to prevent impending biliary and gastric outlet obstruction. Laparoscopic procedures are generally preferred to allow quicker recovery time; therefore, patients can initiate palliative chemotherapy. For distal obstructive tumors in the ileum, diverting ileostomy may be considered. The risks and benefits of palliative surgery must be carefully reviewed by both the surgeon

and medical oncologist in the context of the overall treatment plan and prognosis.

Medical Therapy

Chemotherapy has been increasingly used over the past several decades, despite a limited number of prospective trials. Adjuvant chemotherapy is often considered for resected and locally advanced tumors within 2 to 3 months after surgical resection, given substantial evidence in the colorectal cancer and pancreatic cancer literature. The European Study Group for Pancreatic Cancer (ESPAC) has included patients with ampulla, biliary, and duodenal adenocarcinoma in their study population because the tumor location and biology may share some similarities, but also the rarity of these diseases makes accrual difficult when studied separately. ESPAC-3 trial showed that adjuvant 5-fluorouracil (5FU) or gemcitabine chemotherapy is associated with an OS benefit (43.1 vs. 35.2 months) after adjusting for high-risk features, such as positive lymph nodes and poor differentiation.[54] The median disease-free survival was 19.5 months in the observation group, compared with 23.0 months in the 5FU group and 29.1 months in the gemcitabine group, but most patients had either biliary or ampulla cancers. Radiation has been used in the adjuvant setting for duodenal adenocarcinoma, with treatment trends of up to 17.1% of resected tumors.[24] Concurrent chemotherapy with radiation in the adjuvant setting, however, has not demonstrated survival benefit;[55,56] therefore, routine referral to radiation oncology should be discouraged. Even so, patients who are later deemed responsive to preoperative chemotherapy and radiation may benefit from improved pathologic response at the time of surgery, which could make surgical resection less morbid and more likely to achieve R0 resection. More research regarding these approaches remains to be done. Likewise, there may be role for radiation therapy for those with positive surgical margins, but additional research needs to be done in this arena.

Treatment trends show that ~22 to 42% of patients with SBA currently obtain adjuvant treatment after resection.[2,57] Most data are derived from retrospective studies that have demonstrated a benefit for adjuvant chemotherapy specific to SBA, particularly those with positive lymph nodes, positive margins, or T4 disease.[57,58] There are also retrospective studies, however, that suggest no statistically significant survival benefit,[23,50,51,59] but overlook the distinct baseline characteristics between those not recommended for adjuvant chemotherapy and those who receive adjuvant chemotherapy. For one, the majority of patients who receive adjuvant chemotherapy are high risk, due to positive margins, positive lymph nodes, and poorly differentiated histology with associated high recurrence rates and poor survival. In contrast, those who do not receive adjuvant chemotherapy are likely patients who have a low risk of recurrence, and will have longer survival. Retrospective studies generally combine data from multiple adjuvant treatment regimens, which generally include capecitabine or 5FU, either alone, or in combination with oxaliplatin (CAPOX [capecitabine and oxaliplatin] or FOLFOX [folinic acid, fluorouracil, and oxaliplatin], respectively), cisplatin, or irinotecan, but it is unclear if a specific regimen could indeed have statistically significant outcome benefit if studied alone in a prospective study. Gemcitabine may be only considered for duodenal adenocarcinomas, where there may be biliary or pancreatic features. Randomized controlled trials for adjuvant chemotherapy are urgently needed to confirm the optimal choice, interval, and duration of chemotherapy regimen to be used after initial surgical resection with curative intent.

There are several studies testing systemic chemotherapy for those with unresectable or metastatic disease. A summary of these notable studies is listed in ►**Table 4**. In general, 5FU plus platinum combination is associated with response rates of 42 to 48%, time to progression of 7 to 8 months, and OS exceeding 1 year.[42,60,61] Similarly, capecitabine combined with oxaliplatin yields a response rate of 50%, and median time to progression of 9 to 11 months in those with unresectable or metastatic disease.[62] FOLFOX is the preferred regimen, compared with other combinations with 5-flurouracil, such as with cisplatin, mitomycin, and irinotecan, due to better side effect profile and possibly better results.[61,63,64] Mitomycin and anthracyclines are no longer used routinely. Bevacizumab has also been studied in the metastatic setting but has not shown statistically significant better response rates or survival benefit; this is largely due, however, to insufficient power.[65] The FOLFIRI regimen is considered a reasonable second-line option, with an expected response rate of 20 to 25%, and progression-free survival (PFS) of 3.2 to 5.6 months.[61,63,66] Other agents, such as cetuximab in *KRAS* wild-type patients,[67] and gemcitabine in tumors that reflect more pancreatic–biliary subtypes, have been reported in case series, or as part of larger clinical trials. There are currently no interventional trials that definitively demonstrate both PFS and OS by comparing a specific chemotherapy regimen to a control group in SBA.

While patients can often receive second- and third-line chemotherapies, cumulative toxicity, along with progressive disease usually starts to adversely affect quality of life, and may limit the ability to receive additional lines of therapy. Even so, most palliative chemotherapy regimens are well tolerated, and have extensive safety data from other gastrointestinal cancer literature. With regard to FOLFOX, CAPOX, and FOLFIRI regimens, median chemotherapy cycles range from five to nine cycles before switching or stopping.[60,62,66] Hematologic toxicity is usually the most common reason for treatment delay and dose reductions, but treatment discontinuation is still most likely due to disease progression. In general, chemotherapy for small intestinal cancer is safe, and can be life prolonging in both the adjuvant and palliative setting.

Currently, there are no guidelines regarding the optimal interval for surveillance after adjuvant chemotherapy or treatment assessment while on palliative chemotherapy. National Comprehensive Cancer Network guidelines for colon cancer are likely appropriate, but some groups advocate for a more aggressive approach, with chest X-rays and contrast-enhanced CTs of the abdomen and pelvis performed every 3 months in the first year, and every 6 months in the second year.[59] Subsequent imaging can be done annually for additional 3 to 5 years. There is no sufficient follow-up

Table 4 Palliative chemotherapy regimens used for metastatic or unresectable small bowel adenocarcinoma

References	Study design	Line of therapy	Chemotherapy regimen	Number of patients	Objective response rate	Progression free survival (mo)	Overall survival (mo)
Xiang et al (2012)[60]	Prospective, single arm, China	First	FOLFOX	33	48.5%	7.8	15.2
Overman et al (2009)[62]	Prospective, single arm, United States.	First	CAPOX	30	50.0%	11.3	20.4
Gibson et al (2005)[64]	Prospective, single arm, United States	First	5FU + doxorubicin + mitomycin	38	18.4%	5	8
Aydin et al (2017)[65]	Retrospective, 2 comparison groups, 5 centers, Turkey	First	FOLFOX or FOLFIRI + bevacizumab	12	58.3%	9.6	18.5
			FOLFOX or FOLFIRI	16	43.7%	7.7	14.8
Tsushima et al (2012)[61]	Retrospective, 5 comparison groups, 41 centers, Japan	First	Fluoropyrimidine monotherapy	60	20%	5.4	13.9
			Fluoropyrimidine + oxaliplatin	22	42%	8.2	22.2
			Fluoropyrimidine + irinotecan	11	25%	5.6	9.4
			Fluoropyrimidine + cisplatin	17	38%	3.8	12.6
			Other regimens	22	21%	3.4	8.1
Zaanan et al (2010)[63]	Retrospective, 4 comparison groups, 13 centers, France	First	5FU alone	10	0%	7.7	13.5
			FOLFOX	48	34%	6.9	17.8
			FOLFIRI	19	9%	6.0	10.6
			5FU + cisplatin	16	31%	4.8	9.3
Overman et al (2008)[42]	Retrospective, 2 comparison groups, single center, United States	First	5FU + platinum	29	41.0%	8.7	14.8
			5FU alone or other regimen	51	15.7%	3.9	12
Fishman et al (2006)[71]	Retrospective, multiple comparison groups, single center, Canada	First or second	Fluoropyrimidine monotherapy	15	13.3%	–	–
			Gemcitabine monotherapy	9	33.3%	–	–
			Fluoropyrimidine + gemcitabine	8	50%	–	–
			Platinum-based regimen	7	42.9%	–	–
			Irinotecan-based regimen	12	41.6%	–	–
Zhang et al (2011)[72]	Retrospective, single arm, 3 centers, China	First	5FU or capecitabine + oxaliplatin	34	32.3%	6.3	14.2
Koo et al (2011)[73]	Retrospective, single arm, 1 center, Korea	First	fluoropyrimidine-based chemotherapy	40	11.1%	5.7	11.8
Zaanan et al (2011)[66]	Retrospective, single arm, 13 centers, France	Second	FOLFIRI	28	20.0%	3.2	10.5
Czaykowski and Hui (2007)[74]	Retrospective, single arm, single center, Canada	First	Fluoropyrimidine-based chemotherapy	16	6%	–	15.6
Locher et al (2005)[75]	Retrospective, single arm, single center, France	First	5FU + platinum	20	21%	8	14

Abbreviation: 5FU, 5-fluorouracil.

data to establish the assurance of 5-year survival as cure, though most recurrences do occur in the first 2 years after surgical resection.[51] Recurrence is also rare in stage I disease, and almost never at the anastomosis site, if an R0 resection was achieved. Given that the first recurrent site is likely regional lymph node, liver, or peritoneum,[51] a contrast-enhanced CT scan is likely more valuable than surveillance endoscopies and routine blood tests. There is no reason to undergo upper endoscopy, capsule endoscopy, or more frequent colonoscopy than recommended for colorectal cancer, except as part of a surveillance program for specific genetic syndromes such as FAP and HNPCC. Imaging to assess treatment response to chemotherapy in the metastatic disease is generally up to the treating physician, but evaluation every 2 to 3 months, or four to six cycles of chemotherapy, is certainly appropriate.

Future Directions

Future directions of SBA include more cost-effective screening for patients at high risk for SBA, better surgical techniques to decrease postoperative morbidity for those with resectable disease, and more personalized systemic treatment options for those with metastatic disease. ACG has detailed recommendations for colorectal cancer screening in patients with FAP, HNPCC, and PJS, but no clear evidence for small bowel cancer screening. These high-risk populations constitute a substantial proportion of new cases each year.

Additional cost–benefit analysis would help provide evidence-based guidelines beyond expert opinion regarding the role for advanced upper endoscopy and capsule endoscopy in patients with specific genetic syndromes. Likewise, routine ileal intubation could be recommended for patients with Crohn's disease to screen for ileal adenocarcinoma, if additional research shows benefit.

Prophylactic colectomy is often discussed in patients with FAP and HNPCC, but there is currently no consensus regarding prophylactic resection of the duodenal bulb or even segmental duodenal resection for high-risk patients. Presently, surgery for duodenal adenocarcinoma is technically challenging, due to close proximity to the liver, biliary tract, and pancreas. There has been consideration for total duodenectomy while preserving the pancreas, but thus far, no current techniques can make that safely possible. As the safety and recovery time from these surgeries improve, prophylactic surgeries may become more accepted for those with high-risk genetic syndromes, especially in the presence of large number of precancerous polyps.

With regard to medical treatment, the BALLAD study (NCT02502370) is a phase III randomized controlled trial in France that will be the first prospective study to evaluate adjuvant chemotherapy in SBA. Patients who achieve R0 resection with no residual disease will be randomized to observation, 5FU monotherapy, or FOLFOX combination within 12 weeks after surgery. This study will attempt to answer the open questions of whether there is a role for adjuvant chemotherapy using a well-established adjuvant regimen in colon cancer. Retrospective data thus far have had mixed results, likely due to selection bias and information bias. This study is currently single center and surprisingly includes stages I and IIA patients who are usually not recommended for adjuvant chemotherapy. Accrual may occur more quickly, once other institutions gain interest in this important trial.

With regard to palliative chemotherapy, NCT00433550 is a phase II open-label, multicenter, dose-escalating study sponsored by the National Cancer Institute to optimize dosing, based on UGT1A1 genotype, using triple combination with capecitabine, oxaliplatin, and irinotecan for metastatic or unresectable SBA. Nab-paclitaxel is also being explored in SBA (NCT01730586). In addition, biologic therapy is being studied with traditional chemotherapy. NCT01202409 is a phase II, open-label, single-arm, prospective study at the MD Anderson Cancer Center that has enrolled *KRAS* wild-type patients with advanced small bowel or ampullary adenocarcinoma to undergo palliative chemotherapy with capecitabine, oxaliplatin, and panitumumab. Similarly, NCT01208103 is a phase II study at the same location that has enrolled patients with metastatic small bowel or ampullary adenocarcinoma to under undergo palliative chemotherapy with capecitabine, oxaliplatin, and bevacizumab. Furthermore, erlotinib is being studied in duodenal adenocarcinoma (NCT00987766), but its limited efficacy in pancreatic cancer likely has precluded continual efforts to apply the drug to SBA. Immunotherapy has not yet been evaluated in SBA, but upcoming treatment trials will be underway (NCT02949219, NCT03000179, and NCT02834013), along with provisions to measure PD-1/PD-L1 expression in resected tumors, which also is unknown. There has not been great interest in targeted therapies because SBAs have low rates of *EGFR*, *HER2*, and *BRAF* mutations. Nevertheless, studies that focus on specific driver mutations regardless of tumor type can enroll patients with SBA (NCT02034110, NCT00004074, and NCT00397384).

Overall SBA is a not a well-understood disease, due to its rarity and lack of prospective data in its management. Much of what we know is extrapolated from pancreatic–biliary cancer and colon cancer literature or from small retrospective studies that are vulnerable to bias, inadequate power, and missing data. Recent molecular and genetic data have suggested various targets for treatments, for which clinical trials are currently underway. Even so, there remains an urgent need for a collective effort to improve surveillance, diagnostics, and treatment approaches in SBA.

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